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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,474	06/15/2001	Jin-Woo Kim	DE1272	1592

7590 01/29/2003

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EXAMINER	
MCGARRY, SEAN	

ART UNIT	PAPER NUMBER
1635	11

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/868,474	KIM, JIN-WOO	
	Examiner	Art Unit	
	Sean R McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/30/02(election)* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *3 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8,10 and 12-16* is/are rejected.

7)☒ Claim(s) *2 and 11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1, 2, 4-8 and 10-16 in Paper No. 10, filed 11/08/02 is acknowledged.

Claims 3 and 9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8, 10, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by New England BioLabs Catalog, pages 106-108, 1995.

New England BioLabs Catalog discloses phosphorylated and nonphosphorylated oligonucleotide linkers including linkers for ApaI. The linker disclosed for ApaI is identical to a fragment corresponding to SEQ ID NO: 1 at positions 20-27, for example. The linker is double stranded and therefore comprises both a sense and an antisense strand. Clearly, these linkers, from a supply catalog, are provided in a container, which would meet the limitations of a kit, for example. The prior art meets all of the structural limitations required by the instant claims.

Claim Rejections - 35 USC § 103

Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over New England BioLabs Catalog, pages 106-108, 1995.

New England BioLabs Catalog discloses phosphorylated and nonphosphorylated linkers including linkers for ApaI. The linker disclosed for ApaI is identical to a fragment corresponding to SEQ ID NO: 1 at positions 20-27, for example. Since the known and routinely use purpose of linkers is in the cloning and subcloning of nucleic acid sequences into vectors, to provide unique restriction sites, for example, one in the art would clearly use such linkers in cloning vectors which are routinely used in cells such as E. coli, which has been routinely used in biotech assays and procedures for over twenty years, for example, in the cloning process.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Claims 2 and 11 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 6 and 7 rely upon the use of KCTC 0667BP, which was deposited under the terms of the Budapest Treaty (page 9 of the instant specification). The application however does not address all the requirements of 37 CFR§ 1.808 Furnishing of samples.

(a) A deposit must be made under conditions that assure that:

(1) Access to the deposit will be available during pendency of the patent application making reference to the deposit to one determined by the Commissioner to be entitled thereto under § 1.14 and 35 U.S.C. 122, and

(2) Subject to paragraph (b) of this section, all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent.

Since the claims require the use of the deposited microorganism and it is not clear that the deposited organism would be readily available to one in the art or that the deposited organism could be routinely made based on the specification, the above conditions must be met in order to comply with the provisions of 35 U.S.C. 112, first paragraph.

Claims 7, 10, 13, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7 and 13 both depend from claim 3, which has been withdrawn from consideration in view of the election filed 11/8/02, rendering the claims vague and indefinite.

Claim 10 recites "the sequence of the full or partial mRNA. . ." There is insufficient antecedent basis for this limitation.

Claim 15 recites "the full or partial mRNA transcribed from the protooncogene or fragment of claim 2. . ." There is insufficient antecedent basis for this limitation.

Claims 12 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant invention is drawn to the antisense based therapy or prevention of cancers via the administration of antisense molecules targeted to HCCR SEQ ID NO: 1.

The instant specification discloses the inhibition of cell proliferation of lung carcinoma cells in culture via the antisense molecule SEQ ID NO: 3.

The instant specification fails to provide adequate guidance, working examples, or examples that would show by correlation the practice of the claimed therapeutic and

preventive therapy instantly claimed without the need to engage in undue trial and error experimentation.

The instant specification provides one example in cell culture and provides general guidance for what one in the art might try in an antisense based therapy, but provides no specific guidance for the therapeutic methods instantly claimed. Antisense-based therapy is an unpredictable art where specific guidance is needed. For example, it was known at the time of filing that *in vitro* examples of antisense based therapy can not be predictably extrapolated to *in vivo* environments and further the activity of one particular antisense does not provide predictability for other antisense targeted to the same mRNA target, for example. Jen et al [STEM CELLS Vol. 18:307-319, 2000] Discuss antisense based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al assert "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. [a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have

many obstacles to overcome. Agrawal [TIBTECH, Vol. 14:376-387, October 1996] states the following: " [t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering in the disease process" (page376); "[o]ligonucleotide must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . .[i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is nt clear how relevant this approach is for *in vivo* situations." (Page379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379).Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-antisense effects, investigators are

searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest."; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to

ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*."

Based on the lack examples that demonstrate the invention by correlation and the lack of specific guidance in the specification, which would be required to practice the instant invention in view of the unpredictable nature of antisense therapies as evidenced by the references above, one in the art would be required to practice undue trial and error experimentation. The quantity of experimentation would include the *de novo* identification of antisense oligonucleotides that function in an *in vivo* environment and further the determination of specific treatment protocols for the vast number of diseases embraced within the term cancer, where these diseases vary vastly in there course of disease action and location in the body, for example. Further, one of skill in the art would need to *de novo* determine how to prevent such a vast array of cancers where the instant specification fails to provide any guidance how to prevent any cancer with antisense to HCCR. Furthermore one in the art would need to overcome the obstacles exemplified in the references above for each disease that is contemplated in the instant invention since the instant specification does not provide guidance that addresses these concerns such that one in the art would know, without undue experimentation, how to proceed past these obstacles in the practice of the instant invention, for example.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (703)305-7028. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SRM
January 27, 2003

SEAN McGARRY
PRIMARY EXAMINER
1635